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(54) Title: PHARMACEUTICAL FORMULATION

(57) Abstract

A gel comprises biodegradable microparticles including a wall–forming material that is relatively insoluble at physiological pH, wherein the liquid phase of the gel is aqueous, buffered to physiological pH.

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PHARMACEUTICAL FORMULATION

Field of the Invention

This invention relates to a pharmaceutical formulation. More particularly, it relates to a gel formed from microparticles.

Background of the Invention

The delivery of therapeutic agents to the site of action, in an appropriate formulation, is not easily solved for all drugs. One means of drug delivery comprises formulating the therapeutic agent and, if necessary, a wall-forming material as microparticles, and preferably hollow microcapsules, of defined size, preferably by spray-drying. Suitable procedures are described in, for example, WO-A-9218164, WO-A-9408627 and WO-A-9615814.

Microparticles produced by spray-drying may be soluble, in which case they are particularly adapted for pulmonary administration. They may also be rendered insoluble, by chemical cross-linking or heating, in which case they are particularly adapted for intravascular administration, so that they reach the liver, a tumour site or other desired loci.

Solutions or suspensions of therapeutic agent are not necessarily appropriate for a formulation intended for subcutaneous injection, in order to provide sustained release of the drug. A semi-solid consistency would be desirable.

Summary of the Invention

Surprisingly, it has been discovered that certain materials that are relatively insoluble in water at physiological pH can be formulated into microparticles and provided as a gel. This can be achieved without any chemical modification of the wall-forming material. More particularly, a gel according to the present invention comprises biodegradable microparticles including a wall-forming material that is relatively insoluble at physiological pH, and the liquid phase of the gel is aqueous, buffered to physiological pH.

Without wishing to be bound by theory, it appears that certain materials, of which casein is one, which can be

formulated as a solution, albeit not at pH 7, can be spray-dried to give microparticles or microcapsules that, upon resuspension in a suitable buffer, provide a gel. This gel is suitable for subcutaneous injection, and can provide a therapeutic agent in a sustained release form.

Description of the Invention

Typically, the wall-forming material forms an aqueous solution at a pH below 4 or above 10, i.e. at relatively acid or alkaline pH. The pH of the solution for spray-drying will typically be at least 1 or 2, or no more than 13 or 14.

The wall-forming material is relatively insoluble in water at pH 7. Typically, it will be insoluble at this pH, to the extent that no sufficiently concentrated solution could be made of it, that would be worth using, for spray-drying on a commercial scale. Such materials include biodegradable natural or synthetic polymers, and other stabilising and suspending agents, including those with haemostatic properties. For example, alginates and oxidised celluloses, pectins and xanthan gums, are soluble at a pH other than physiological pH, and are known for their haemostatic properties, upon contact with water. More particularly, the material may be a protein such as casein. Casein is a protein derived from milk, having a molecular weight in the region of 23,000; it is sparingly soluble in water but is soluble in aqueous alkali.

The wall-forming material may itself be a therapeutic agent. Alternatively, a therapeutic agent is added, e.g. in the formulation from which the microparticles are formed. Suitable agents include insulin, hormones, cytotoxic agents, antibiotics, antivirals, analgesics and anti-inflammatory agents; it will be readily apparent to the skilled person that any suitable agent can be used.

Spray-drying may be conducted by procedures that are generally known, and are described in more detail in the Andaris publications given above (the contents of which are incorporated herein by reference). The hollow or other microcapsules that can be produced by this technology can have any desired characteristics, according to the

conditions that are chosen. The size and size distribution of the microparticles are not especially critical, for the purposes of this invention.

In order to prepare the gel, the microparticles are resuspended in an appropriate buffer, to physiological pH. Any suitable buffer may be chosen, provided that it is physiologically-acceptable. For example, if the therapeutic agent is alkaline, a phosphate-citrate buffer may be chosen.

The materials etc. that are used in this invention may have some effect on the ability of the microparticles to form a gel, upon resuspension in buffer. Based on the information provided in this specification, one of ordinary skill in the art can readily determine whether or not a suitable gel can be formed.

The release characteristics of products of this invention may be manipulated by controlling the feedstock formulation prior to spray-drying. Alternatively, or in addition, the microparticles and/or the gel may be further stabilised, e.g. by the use of chemical cross-linking agents or the addition of viscosity enhancers.

The following Example illustrates the invention.

Example

50 g casein (Sigma, Technical grade) was dissolved in 250 ml 0.5 M NaOH; the pH was determined to be 13.4. Myoglobin (Sigma, Horse heart) was selected for use as a marker, and as representative of a therapeutic agent to be released: 1 g was dissolved in 20 ml purified water, and a 1 ml aliquot was removed for the preparation of standards. The remaining 19 ml was added to the casein solution prior to spray-drying. The feed solution was continually stirred during spray-drying, which was conducted under the following conditions:

Inlet temperature	220°C
Outlet temperature	83°C
Atomisation pressure	5.0 bar
Feed rate	12.5 g/min
Product recovery	51.3%

The resultant microcapsules were deep red in colour and appeared to be fairly cohesive.

Resuspension of the microcapsules in low concentration phosphate buffer (pH 7) proved unsuccessful as the microcapsules were found to dissolve; the reason is that the buffer was insufficiently concentrated to overcome the high pH of the microcapsules. Upon resuspension of 1 g spray-dried material in 6 ml of phosphate-citrate buffer (0.15 M, pH 5.0), a gel was formed. The gel was found to increase in strength over a period of 30 minutes as determined visually.

Three 1 g aliquots of the spray-dried microcapsules were placed into universal tubes. 10 ml phosphate-citrate buffer was added to each tube and the samples vortexed. A gel was formed immediately in each of the tubes. The tubes were then centrifuged (3 min @ 3000 rpm) and the whole supernatants removed. The supernatants were diluted 1:1 before scanning between 500 and 700 nm. A 0.5 mg/ml standard of the myoglobin was scanned at the same wavelengths and used to determined the levels of myoglobin released initially on contact of the microcapsules with water.

Fresh 5 ml aliquots of the phosphate-citrate buffer were added to each of the gels and the samples were placed in a water bath at 37°C. At various timepoints, samples were removed from the water bath and centrifuged. The supernatants were diluted 1:1 and scanned as before. 5 ml aliquots of phosphate-citrate buffer were added to the centrifuged gels at each timepoint before placement back in the water bath. The results showed that myoglobin was retained to some extent.

By way of example, increasing the concentration of casein in the feedstock, e.g. to 30% w/v, may increase the strength of the gel. The same effect may be achieved by dissolution of casein at different values of pH.

CLAIMS

1. A gel comprising biodegradable microparticles including a wall-forming material that is relatively insoluble at physiological pH, wherein the liquid phase of the gel is aqueous, buffered to physiological pH.

2. A gel according to claim 1, wherein the microparticles consist essentially only of a therapeutic agent and the wall-forming material.

3. A gel according to claim 1 or claim 2, wherein the microparticles include is a biodegradable natural or synthetic polymer.

4. A gel according to any preceding claim, wherein the microparticles include a stabilising or suspending agent having haemostatic properties.

5. A gel according to any preceding claim, wherein the microparticles include a protein.

6. A gel according to any preceding claim, wherein the microparticles include casein.

7. A gel according to any preceding claim, wherein the microparticles are obtainable by spray-drying from an aqueous solution having a pH below 4 or above 10.

8. A method for the preparation of a gel according to any preceding claim, which comprises spray-drying an aqueous solution as defined in claim 7, and reconstituting the resultant microparticles in said buffer.